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RESEARCH ARTICLE

The CryoPop study: Screening for high-grade cervical dysplasia in Karnataka, India

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Abstract

Objective: To describe our experience of screening with visual inspection with acetic acid (VIA) and colposcopy to identify women with high-grade precancerous cervical lesions who were candidates for cryotherapy. Women were screened to determine eligibility for a clinical trial testing the safety and efficacy of a new, simple and inexpensive cryotherapy device (CryoPop®) targeted for use in low and middle-income countries (LMICs).

Design: Prospective cohort study.

Setting: Primary and urban health centres in Belagavi, Hubballi and Vijayapur, India.

Population: Women in the age-group 30–49 years, premenopausal, with no prior hysterectomy and no known HIV infection were eligible for screening.

Methods: Visual inspection with acetic acid was performed on eligible women following informed consent. VIA-positive women were referred for colposcopy and biopsy. Biopsies were read by two pathologists independently, with a third pathologist acting as tie-breaker if needed.

Main outcome measures: The primary outcome measures were the number/proportion of women screening positive by VIA and the number/proportion of those women screening VIA-positive found to have high-grade cervical lesions on biopsy (cervical intraepithelial neoplasia 2/3 [CIN 2/3]). Demographic variables were compared between women who screened VIA-positive and those who screened VIA-negative; a separate comparison of demographic and limited reproductive variables was performed between women who had CIN 2/3 on biopsy and those without CIN 2/3 on biopsy. Chi-square or Fisher's exact tests for categorical data and *t*-tests or analysis of variance for numeric data were used with all tests two-sided and performed at an alpha 0.05 level of statistical significance.

Results: A total of 9130 women were screened with VIA between 4 July 2020 and 31 March 2021. The mean age of all women screened was 37 years (standard deviation = 5.6 years) with 6073 of the women (66.5%) in the 30–39 year range. Only 1% of women reported prior cervical cancer screening. A total of 501 women (5.5%) were VIA-positive; of these, 401 women underwent colposcopy. Of those who had

The CryoPop Study Group members are presented in Appendix 1.

colposcopy, 17 (4.2%) had high-grade lesions on biopsy, an additional 164 (40.9%) had low-grade cervical lesions on biopsy or endocervical curettage and one woman (0.2%) was found to have invasive cancer. VIA-positive women were younger and had higher levels of education and income; however, women who were VIA-positive and found to have CIN 2/3 were older, were more likely to be housewives and had higher household income than those without CIN 2/3.

Conclusion: Despite the COVID-19 pandemic, over 9100 women were screened with VIA for precancerous lesions. However, only 17 (4.2%) were found to have biopsy-proven high-grade cervical lesions, underscoring the subjective performance of VIA as a screening method. Given that this is significantly lower than rates reported in the literature, it is possible that the prevalence of high-grade lesions in this population was impacted by screening a younger and more rural population. This study demonstrates that screening is feasible in an organised fashion and can be scaled up rapidly. However, while inexpensive and allowing for same-day treatment, VIA may be too subjective and have insufficient accuracy clearly to identify lesions requiring treatment, particularly in low-prevalence and low-risk populations, calling into question its overall cost-effectiveness.

KEYWORDS
cervical cancer, cryotherapy, India, screening, VIA

1 | INTRODUCTION

Globally, cervical cancer is the fourth most common cancer in women. Approximately 90% of cervical cancer deaths occur in low- to middle-income countries (LMICs), which have only 5% of the global cancer resources and lack screening, follow-up and investment in preventive services.[1] Cervical cancer is relatively unique in that there is a recognisable pre-invasive phase in which progression from human papilloma virus (HPV) infection – the primary causative agent of cervical cancer – to invasive disease evolves over several years, passing through distinct precancerous phases. This prolonged natural history offers an extended window to detect the presence of precancerous lesions, which, when promptly treated, prevents progression to invasive cancer. In November 2020, the World Health Organization (WHO) launched its global strategy and targets for the elimination of cervical cancer. The goal to be achieved by year 2030 includes 70% of women screened using a high-performance test by the age of 35 and again by the age of 45, and treating 90% of those with precancerous changes.[2] Scalable screening and cost-effective treatment technologies will be required to meet this ambitious goal.

In 2013, the National Cancer Institute (NCI) launched the Affordable Cancer Technologies (ACT) programme and called for proposals targeting cancer prevention and control in LMICs. The objective was to support the development of low-cost, easy-to-use screening, diagnostic and treatment tools that could feasibly be implemented in low-resource settings.

As one of the initial projects funded under this programme, the CryoPop® study is a clinical trial testing the safety and efficacy of a new, simple and inexpensive cryotherapy device, using the liquid state of CO_2 to form dry ice as the freezing element. CryoPop® is specifically targeted for use in LMICs for the treatment of precancerous cervical lesions. Phase 1 of the CryoPop® study was performed in the Philippines, which assessed performance characteristics and depth of necrosis with CryoPop®, compared with standard cryotherapy equipment in women with normal cervical cytology and undergoing hysterectomy. This research activity in India is Phase 2 of the CryoPop® study and was designed to test the CryoPop Cryopen® device in women with abnormal cervical cytology. To optimise evaluation of effectiveness and enable comparison with historical data on cryotherapy, the decision was made to treat only histologically proven high-grade cervical lesions (CIN 2/3). In most LMICs, cytological screening is not widespread or feasible and, when it occurs, is ad hoc and not organised[3]; Visual Inspection with Acetic Acid (VIA) was chosen for initial screening in phase 2 study, and women who were VIA-positive were referred for colposcopy and biopsy.

This paper describes our experience with screening with VIA and colposcopy for VIA-positive women in order to identify candidates for enrolment in the CryoPop® study testing the safety and efficacy of a new cryotherapy device.

2 | METHODS

2.1 | Recruitment

The study was conducted in India through the KLE Academy of Higher Education and Research (KAHER) at the Jawaharlal Nehru Medical College (JNMC) in Belagavi; at Karnataka Institute of Medical Sciences (KIMS); The Karnataka Cancer Therapy and Research Institute (KCTRI) in Hubballi; and Shri B. M. Medical College (BLDE) in Vijayapur, Karnataka,

in collaboration with Jhpiego Corporation, a global affiliate of Johns Hopkins University in Baltimore (MD, USA). Women were recruited at 39 centres providing primary healthcare to rural and urban populations in Belagavi, Hubballi and Vijayapur from July 2020 through April 2021. In addition, screening camps were implemented to enhance the ability to screen larger numbers of women in a shorter period of time. Community sensitisation and awareness sessions were conducted in the study areas prior to recruitment by Accredited Social Health Activists (ASHAs), a community healthworker cadre. Each ASHA worker covers a population of about 1000 people. Posters and/or flyers outlining the study in Hindi, Marathi and Kannada as well as English were posted in appropriate areas in the hospitals and health centres. Women were eligible for screening if they met the following criteria: age 30–49; premenopausal; no prior hysterectomy; not known to be HIV-infected.

2.1.1 | Procedures

VIA was performed on eligible women consenting to screening by trained research nurses. VIA-positive women were referred for colposcopy and biopsy at one of the tertiary medical centres listed above. A few colposcopies were performed in the health centres in Belagavi during the COVID-19 pandemic in an effort to improve follow-up of VIA-positive women. Transportation was provided and women were accompanied by ASHAs. A point-of-care urine pregnancy test was performed at the time of colposcopy. Those women who tested positive were excluded from the study. At the time of evaluation, VIA-positive patients were counselled about the possible treatment options available, pending colposcopically guided biopsy results.

2.1.2 | Outcome measures

The primary outcome measures were the number/proportions of women screening positive by VIA and the number/proportion of those women screening VIA-positive found to have CIN 2+ on cervical biopsy. Individual variables obtained included age, marital status, education level, occupation, monthly income, pregnancy history, contraception use and history of prior cervical cancer screening.

2.1.3 | Statistical analysis

Demographic data were described for categorical data and means and standard deviations (SD) for numeric data. Biopsy results were summarised overall and by demographic characteristics. Demographic variable distribution was compared between women who screened VIA-positive and those who screened VIA-negative; a separate comparison of demographic and limited reproductive variables was performed between women who had CIN 2/3 on biopsy and those without CIN 2/3 on biopsy. Chi-square tests were used for categorical data and *t*-tests for numeric data. Statistical analyses were performed using STATA statistical software programme (StataCorp. 2021; Stata Statistical Software: Release 17; StataCorp LLC.) All tests were two-sided and were performed at a 0.05 level of statistical significance.

2.1.4 | IRB approval

IRB approval was obtained through the Johns Hopkins School of Public Health, the Indian Council of Medical Research (ICMR), and state and local ethics review boards in the state of Karnataka, India. Written consent was obtained from all the participating women in the study.

3 | RESULTS

A total of 9130 women were screened with VIA between 4 July 2020 and 31 March 2021 (see Table 1: Characteristics of women screened with VIA). Of these, 4540 (49.7%) were screened at KLE, 1927 (21.1%) at KCTRI, 1446 (15.8%) at BLDE, and 1217 (13.3%) at KMC. Of the total of 9130 women, 4649 were screened after onset of the second COVID-19 wave in February 2021. The mean age of all screened was 37 years (SD = 5.6 years) with 6073 of the women (66.5%) in the 30- to 39-year range. The majority of women, 8647 (94.7%), were married and living with their husbands. Of all of those screened, 2649 (29.0%) had no formal schooling and 3498 (38.3% had only a primary school education. Although the majority of women (4601, 50.4%) were housewives, a substantial number worked as labourers (3230, 35.4%). Only 1% of women reported prior cervical cancer screening.

A total of 501 women (5.5%) were VIA-positive and were referred for colposcopy. Women who screened positive on VIA were younger (mean 36.17 [SD 5.17] versus 37.10 years [SD 5.61]; $P < 0.001$), more educated (post-secondary education: 8.4% among those screening positive versus 6% among those screening negative; $P < 0.001$), more likely to be salaried professionals (12.2% among those screening positive versus 8.8% those screening negative; $P < 0.001$) and more likely to have higher income (Rs. ≥15 000, 8% among those screening positive versus 6.2% among those screening negative; $P = 0.036$).

Of the 501 women who were VIA-positive, 400 (79.8%) presented for colposcopy. In addition, one woman was referred to the study directly for a colposcopically directed biopsy that showed a high-grade lesion (CIN 2/3). Of the 401 women who underwent colposcopy, 17 (4.2%) had biopsy-proven CIN 2/3 and were eligible for enrolment in the CryoPop® study. An additional 164 (40.9%) had low-grade cervical lesions on biopsy or electrocardiogram (ECC). One woman (0.2%) was found to have invasive cancer and was referred for appropriate treatment. A total of 219 (54.6%) women had a negative biopsy ($n = 136$) or negative findings at the time of colposcopy ($n = 83$) and no biopsies or ECC were performed. Women

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TABLE 1 Characteristics of women screened with visual inspection with acetic acid.

	Normal, $n=8629$	Abnormal, $n=501$	Total, $n=9130$	p-Value
Site				
SBMMC Vijayapur	1349 (15.6%)	97 (19.4%)	1446 (15.8%)	0.003[a]
KCTRI Hubballi	1850 (21.4%)	77 (15.4%)	1927 (21.1%)	
JNMC Belagavi	4274 (49.5%)	266 (53.1%)	4540 (49.7%)	
KIMS Hubballi	1156 (13.4%)	61 (12.2%)	1217 (13.3%)	
Age, mean (SD)	37.10 (5.61)	36.17 (5.17)	37.05 (5.59)	<0.001[b]
Age category, years				
30–34	3237 (37.5%)	211 (42.1%)	3448 (37.8%)	0.002[a]
35–39	2464 (28.6%)	161 (32.1%)	2625 (28.8%)	
40–44	1632 (18.9%)	75 (15.0%)	1707 (18.7%)	
45–49	1296 (15.0%)	54 (10.8%)	1350 (14.8%)	
Household size	5.3 (2.8)	5.3 (3.1)	5.3 (2.8)	0.78[b]
Marital status				
Unmarried	18 (0.2%)	1 (0.2%)	19 (0.2%)	0.17[a]
Married and living with husband	8166 (94.6%)	481 (96.0%)	8647 (94.7%)	
Married but husband away	100 (1.2%)	5 (1.0%)	105 (1.2%)	
Separated/divorced	28 (0.3%)	0 (0.0%)	28 (0.3%)	
Widowed	315 (3.7%)	13 (2.6%)	328 (3.6%)	
Refused to answer	2 (0.0%)	1 (0.2%)	3 (0.0%)	
Education level				
No formal schooling	2521 (29.2%)	128 (25.5%)	2649 (29.0%)	<0.001[a]
Primary	3326 (38.5%)	172 (34.3%)	3498 (38.3%)	
Secondary	2255 (26.1%)	157 (31.3%)	2412 (26.4%)	
Post-secondary	521 (6.0%)	42 (8.4%)	563 (6.2%)	
Refused to answer	6 (0.1%)	2 (0.4%)	8 (0.1%)	
Current occupation				
Housewife	4352 (50.4%)	249 (49.7%)	4601 (50.4%)	<0.001[a]
Salaried professional	763 (8.8%)	61 (12.2%)	824 (9.0%)	
Self-employed	441 (5.1%)	28 (5.6%)	469 (5.1%)	
Labourer	3070 (35.6%)	160 (31.9%)	3230 (35.4%)	
Refused to answer	3 (0.0%)	3 (0.6%)	6 (0.1%)	
Family income				
< Rs. 5000	4676 (54.2%)	240 (47.9%)	4916 (53.8%)	0.036[a]
Between Rs. 5000 and Rs. 10000	1976 (22.9%)	128 (25.5%)	2104 (23.0%)	
Between Rs. 10000 and Rs. 15000	791 (9.2%)	42 (8.4%)	833 (9.1%)	
Between Rs. 15000 and Rs. 20000	303 (3.5%)	23 (4.6%)	326 (3.6%)	
> Rs. 20000	230 (2.7%)	17 (3.4%)	247 (2.7%)	
Refused to answer	653 (7.6%)	51 (10.2%)	704 (7.7%)	
History of cervical cancer screening				
No	8535 (98.9%)	491 (98.0%)	9026 (98.9%)	0.063[a]
Yes	94 (1.1%)	10 (2.0%)	104 (1.1%)	
Menopause status				
No	8500 (98.5%)	496 (99.0%)	8996 (98.5%)	0.37[a]
Yes	129 (1.5%)	5 (1.0%)	134 (1.5%)	

(Continues)

TABLE 1 (Continued)

	Normal, $n=8629$	Abnormal, $n=501$	Total, $n=9130$	p-Value
Current use of tobacco				
I have never chewed or smoked tobacco	8414 (97.5%)	488 (97.4%)	8902 (97.5%)	0.52[a]
I stopped chewing or smoking tobacco within the past 1 year	15 (0.2%)	2 (0.4%)	17 (0.2%)	
I chew or smoke tobacco regularly	200 (2.3%)	11 (2.2%)	211 (2.3%)	

[a]Pearson's chi-square test.
[b]Two-sample t-test.

with CIN 2/3 were older (mean age 38.2 years, SD 5.16) than those with CIN 1 (mean age 35.3, SD 4.51) or those with negative findings (mean age 36.5, SD 5.42; $P=0.015$). Women diagnosed with CIN 2/3 were more likely to be housewives (71%) compared with women with normal or no biopsy (55%) or women with CIN 1 (40%; $P<0.001$). High-grade lesion was also associated with higher income (18% in the >20 000 Rs category) compared with 3% in the negative biopsy group and 2% in the low-grade lesion group ($P=0.030$). The primary reason for not presenting for colposcopy was concern about COVID-19; the second most common reason was lack of permission from husband or mother-in-law (see Table 2 for variables in women who were VIA-positive and received colposcopy, by histopathology results).

4 | DISCUSSION

Despite the COVID-19 pandemic, over 9100 women were screened with VIA for precancerous lesions. In preparation for the study, it was projected that 10 000 women would require screening to identify 100 with CIN 2/3, based on prior literature regarding VIA and the presence of high-grade lesions and on prior experience with VIA in India.[4] However, only 17 (4.2%) women were found to have biopsy-proven CIN 2/3.

4.1 | Strengths/limitations

The team was able to screen a large number of women in a short period of time, despite implementation during the COVID-19 pandemic. Screening was facilitated by investigators/clinical staff who were experienced with VIA, the use of screening camps to increase volume, and the use of ASHAs. This unique community worker cadre is employed by the Indian Ministry of Health and Family Welfare (MoHFW) within its National Rural Health Mission (NRHM) to connect marginalised communities across India and help them enter and navigate the healthcare system.

Nevertheless, the COVID-19 pandemic did have a significant impact on recruitment and screening. There were delays due to COVID-19 surges and lockdowns in both USA and India, with temporary cessation of all research and an increase in potential participant anxiety. With the initial surge, study procedures were paused for 2 weeks to develop and ensure robust infection prevention procedures at all points of contact. India experienced its first lockdown in late March 2020, with phased reopening starting in July 2020 and a second COVID-19 surge and lockdown beginning at the end of February 2021. No staff or participants tested positive for COVID-19 during the study. Vaccines became available in January 2021 and most staff had at least one dose by the study end. Nevertheless, screening camps had to reduce numbers of women screened at each time point and the ASHAs, who were critical to community sensitisation and accompanied women to colposcopy, were diverted to COVID-19-related activities. Despite precautions, over 100 women who needed colposcopy could not be convinced to come for this procedure, largely because it required travelling to hospital centres which were designated COVID-19 care facilities and the women did not feel safe going there.

Because India currently does not have an organised and routine cervical cancer screening system, VIA was chosen because it is simple, inexpensive and the screening test of choice in India[5]; results are available within minutes, eliminating the need for recall and preventing loss to follow-up. A review of published studies of VIA accuracy with histology as the standard and CIN 2 as the outcome measure, found a sensitivity of 79–82% and a specificity of 91–92%, with PPV 9–10%.[6] However, a recent systematic review and meta-analysis suggested that the effectiveness of VIA in preventing invasive cervical cancer is inconclusive.[7] VIA is inherently subjective, is less sensitive when the entire squamocolumnar junction is not visible and may be impacted by lack of provider experience, acetic acid of insufficient strength or when examination is performed too soon (or too late) after application. Another limitation is that women who were VIA-positive and had colposcopy that revealed no abnormalities often did not have a biopsy or ECC performed; it is possible that some of these women had CIN 2/3 that was not identified. A final limitation was a failure sufficiently to engage the husbands, who have a primary decision-making role in the family, in community education and sensitisation.

4.2 | Interpretation

Although we were able to screen a large number of women in a short amount of time, we found far fewer histologically confirmed high-grade cervical lesions than anticipated.

TABLE 2 Participant characteristics by colposcopically directed biopsy results.

	Normal/Not done, $n=219$	High-grade lesion, $n=17$	Low grade lesion, $n=164$	Cancer, $n=1$	Total, $n=401$	p-Value[a]
Age, mean (SD)	36.53 (5.42)	38.18 (5.16)	35.30 (4.51)	30.00	36.08 (5.10)	0.015[c]
Age category, years						
30–34	91 (41.6%)	3 (17.6%)	76 (46.3%)	1 (100.0%)	171 (42.6%)	0.031[d]
35–39	64 (29.2%)	8 (47.1%)	59 (36.0%)	0 (0.0%)	131 (32.7%)	
40–44	35 (16.0%)	4 (23.5%)	19 (11.6%)	0 (0.0%)	58 (14.5%)	
45–49	29 (13.2%)	2 (11.8%)	10 (6.1%)	0 (0.0%)	41 (10.2%)	
Household size, mean (SD)	5.5 (3.8)	4.9 (1.6)	5.2 (2.7)	2.0	5.4 (3.3)	0.62[c]
Marital status						
Married and living with husband	208 (95.0%)	17 (100.0%)	159 (97.0%)	1 (100.0%)	385 (96.0%)	0.82[d]
Married but husband away	4 (1.8%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	5 (1.2%)	
Widowed	6 (2.7%)	0 (0.0%)	4 (2.4%)	0 (0.0%)	10 (2.5%)	
Refused to answer	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
Education level						
No formal schooling	56 (25.6%)	2 (11.8%)	37 (22.6%)	0 (0.0%)	95 (23.7%)	0.21[d]
Primary	85 (38.8%)	7 (41.2%)	49 (29.9%)	1 (100.0%)	142 (35.4%)	
Secondary	60 (27.4%)	7 (41.2%)	60 (36.6%)	0 (0.0%)	127 (31.7%)	
Post-secondary	16 (7.3%)	1 (5.9%)	18 (11.0%)	0 (0.0%)	35 (8.7%)	
Refused to answer	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	
Current occupation						
Housewife	120 (54.8%)	12 (70.6%)	66 (40.2%)	1 (100.0%)	199 (49.6%)	<0.001[d]
Salaried professional	28 (12.8%)	4 (23.5%)	19 (11.6%)	0 (0.0%)	51 (12.7%)	
Self-employed	10 (4.6%)	1 (5.9%)	8 (4.9%)	0 (0.0%)	19 (4.7%)	
Labourer	58 (26.5%)	0 (0.0%)	71 (43.3%)	0 (0.0%)	129 (32.2%)	
Refused to answer	3 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	
Family income						
< Rs. 5000	87 (39.7%)	7 (41.2%)	93 (56.7%)	0 (0.0%)	187 (46.6%)	0.030[d]
Between Rs. 5000 and Rs. 10 000	55 (25.1%)	4 (23.5%)	50 (30.5%)	0 (0.0%)	109 (27.2%)	
Between Rs. 10 000 and Rs. 15 000	27 (12.3%)	0 (0.0%)	11 (6.7%)	0 (0.0%)	38 (9.5%)	
Between Rs. 15 000 and Rs. 20 000	8 (3.7%)	1 (5.9%)	6 (3.7%)	0 (0.0%)	15 (3.7%)	
> Rs. 20 000	7 (3.2%)	3 (17.6%)	4 (2.4%)	1 (100.0%)	15 (3.7%)	
Refused to answer	35 (16.0%)	2 (11.8%)	0 (0.0%)	0 (0.0%)	37 (9.2%)	
Current use of tobacco						
I have never chewed or smoked tobacco	217 (99.1%)	16 (94.1%)	160 (97.6%)	1 (100.0%)	394 (98.3%)	0.11[d]
I stopped chewing or smoking tobacco within the past 1 year	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
I chew or smoke tobacco regularly	1 (0.5%)	1 (5.9%)	4 (2.4%)	0 (0.0%)	6 (1.5%)	
History of pregnancy						
No	4 (1.8%)	0 (0.0%)	3 (1.8%)	1 (100.0%)	8 (2.0%)	1.00[d]
Yes	215 (98.2%)	17 (100.0%)	161 (98.2%)	0 (0.0%)	393 (98.0%)	

(Continues)

TABLE 2 (Continued)

	Normal/Not done, $n=219$	High-grade lesion, $n=17$	Low grade lesion, $n=164$	Cancer, $n=1$	Total, $n=401$	p-Value[a]
Gravidity						
One	13 (5.9%)	0 (0.0%)	11 (6.7%)	0 (0.0%)	24 (6.0%)	0.51[b]
Two	79 (36.1%)	6 (35.3%)	68 (41.5%)	0 (0.0%)	153 (38.2%)	
Three	86 (39.3%)	10 (58.8%)	57 (34.8%)	0 (0.0%)	153 (38.2%)	
Four	27 (12.3%)	0 (0.0%)	18 (11.0%)	0 (0.0%)	45 (11.2%)	
Five or more	10 (4.6%)	1 (5.9%)	7 (4.3%)	0 (0.0%)	18 (4.5%)	
Missing	4 (1.8%)	0 (0.0%)	3 (1.8%)	1 (100.0%)	8 (2.0%)	
Number of living children						
One	17 (7.8%)	0 (0.0%)	25 (15.2%)	0 (0.0%)	42 (10.5%)	0.049[b]
Two	95 (43.4%)	7 (41.2%)	74 (45.1%)	0 (0.0%)	176 (43.9%)	
Three	80 (36.5%)	9 (52.9%)	44 (26.8%)	0 (0.0%)	133 (33.2%)	
Four	17 (7.8%)	1 (5.9%)	16 (9.8%)	0 (0.0%)	34 (8.5%)	
Five or more	5 (2.3%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	6 (1.5%)	
None	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (0.5%)	
Missing	4 (1.8%)	0 (0.0%)	3 (1.8%)	1 (100.0%)	8 (2.0%)	
Current use of birth control						
No	83 (37.9%)	7 (41.2%)	48 (29.3%)	1 (100.0%)	139 (34.7%)	0.14[d]
Yes	131 (59.8%)	10 (58.8%)	116 (70.7%)	0 (0.0%)	257 (64.1%)	
Don't know/refused to answer	5 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.2%)	
Birth control method						
Copper IUD	0 (0.0%)	1 (5.9%)	1 (0.6%)	0 (0.0%)	2 (0.5%)	0.029[d]
Barrier	6 (2.7%)	0 (0.0%)	16 (9.8%)	0 (0.0%)	22 (5.5%)	
Injectable	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (0.5%)	
Oral contraceptive pills	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
Tubal ligation (tubectomy)	122 (55.7%)	9 (52.9%)	98 (59.8%)	0 (0.0%)	229 (57.1%)	
Other	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
Missing	88 (40.2%)	7 (41.2%)	48 (29.3%)	1 (100.0%)	144 (35.9%)	
Colposcopic findings						
Normal	96 (43.8%)	1 (5.9%)	9 (5.5%)	0 (0.0%)	106 (26.4%)	<0.001[d]
Low-grade lesion	111 (50.7%)	14 (82.4%)	135 (82.3%)	1 (100.0%)	261 (65.1%)	
High-grade lesion	11 (5.0%)	2 (11.8%)	20 (12.2%)	0 (0.0%)	33 (8.2%)	
Suspicious for cancer	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	

[a]One patient with cancer was excluded when calculating the reported *P*-values.
[b]Kruskal–Wallis test.
[c]One-way analysis of variance.
[d]Fisher's exact test.

The rate of VIA-positive screening overall was 5.5%, consistent with other studies performed in LMICs without endemic HIV.[8–10] There was consistent attention to rates of VIA positivity over the course of the study; standardised VIA practice using image flashcards was created and remedial sessions held to review VIA performance and interpretation.

One-fifth of women who screened VIA-positive, did not come for colposcopy and were lost to follow-up. Despite the number of women screened and the incidence of cervical cancer in India, it is likely that the prevalence in this population, in which the majority of the women were married, lived in rural areas and had a mean age of 37 years, was lower than would be seen in older and more urban populations, where earlier sexual intimacy and more partners, smoking and other changes in lifestyle impact the risk of HPV infection.[11] An additional consideration is that 41% of those who were VIA-positive had low-grade lesions on biopsy. Cases of histological low-grade CIN (CIN grade 1) are associated with high rates of regression and low rates of

progression, and observation rather than treatment is recommended.[12] However, in LMICs where routine cervical screening is not the norm and where, even when screening is possible, it may occur only once in a woman's lifetime, perhaps treating these lesions may be more reasonable and would improve considerations of cost-effectiveness when screening with VIA.

5 | CONCLUSION

Cervical cancer is the second most common cancer in women aged 15–44 years in India, their peak years of reproductive life and productivity. In 2020, cervical cancer accounted for 9.4% of all cancers and 18.3% (123 907) of new cases in India.[13] Healthcare resources are scarce, especially in more rural areas, and late diagnosis is common. A recent Health Technology Assessment in 2021 for early diagnosis of cervical cancer concludes that among various screening strategies, VIA every 5 years is the most cost-effective screening method in the context of India.[14]

The Government of India (GOI) has paid careful attention to cervical cancer prevention since 2013, with operational guidelines for screening and prevention and evidence regarding cancer screening in countries with established and organised screening programmes. Healthcare workers across the country were trained in knowledge and skills related to screening using an ECHO (Extension for Community Healthcare Outcomes) model. However, the ability of the GOI to implement large-scale screening is challenged by poor infrastructure, a low number of healthcare workers, as well as poor knowledge about cervical cancer, embarrassment, anxiety and stigma on the part of women.[15] Van Dyne et al.[16] conducted a study to establish baseline cervical cancer screening coverage in India, which reported only 29.8% of women being screened and a prevalence of screening higher in the urban areas. The diagnosis of invasive cervical cancer was usually based on opportunistic screening or after the onset of the symptoms.[17] In a 2021 India factsheet, the coverage of cervical cancer screening coverage was reported to be only 3.1% and was lowest in rural areas.[18]

This study demonstrates that screening is feasible in an organised fashion and can be scaled up rapidly. A recent review found that community health workers can increase community awareness and assist in cancer screening and follow-up, as well as enhancing acceptability.[19] India's longstanding cadre of community health workers (ASHAs) were invaluable in this study and would be indispensable in a widespread screening programme. However, the findings also suggest that, although inexpensive and allowing for same-day treatment, VIA may be too subjective and have insufficient accuracy clearly to identify lesions requiring treatment and may result in significant over-treatment, particularly in low-prevalence and low-risk populations, calling into question its overall cost-effectiveness. A true point-of-care HPV test that is affordable and has high precision (with the potential for self-collection) would provide more objective, acceptable and sensitive results. This approach is now recommended as the primary screening test by WHO,[20] using either a screen-and-treat approach or a screen-, triage- and treat approach, in which triage could entail partial genotyping, colposcopy, or VIA or cytology. However, both cost and ability to achieve rapid results with HPV testing remain a challenge.

Finally, some women opt against proceeding to colposcopy due to lack of permission from their husbands. points to the importance of keeping cultural contexts in mind when planning and implementing studies.

Although we were able to screen a large number of women, even in the midst of a global pandemic, COVID-19 continues to evolve and affect all parts of our lives. The diversion of healthcare resources and workers, shutdowns and the anxiety of patients who may avoid the healthcare system has disrupted many services in both high-income and in LMICs. To prevent further increases in cervical cancer burden, it is crucial that governments and health systems work to ensure the continuation and expansion of efforts for prevention of cervical cancer.

AUTHOR CONTRIBUTIONS

AD is the country principal investigator and contributed to the development and implementation of the study protocol and drafting the paper. SY is the country research coordinator and contributed to the drafting of the study protocol and development of the paper. JRA is the principal investigator and was instrumental in grant proposal, conception and development of the protocol and drafting and finalising the paper. EL is a co-investigator and contributed to the review and finalisation of the paper. SSG and RD contributed to the study concept as well as reviewing the study protocol and finalising the paper. GY and AR were involved in developing and finalising the statistical framework for the study. GY performed the final analyses of the results. CW contributed to early analysis and resolving data questions. MM led the study protocol development process and the study site preparation. AB, BP, EK, HP, KD, LL, MN, MBB, MRG, PR, RW, RA, RC, RK, SC, SB, SV, SH, VP and SY were critically involved implementing the study and contributed to drafting the paper. KT is the US research coordinator and was involved in implementation and quality assurance activities. All authors have read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The following Institutional Review Boards or Ethics Committees provided approvals for the study: Johns Hopkins School of Public Health (JHSPH) Institutional Review Board (IRB) IRB No 8491; Institutional Ethics Committee, KLE Academy of Higher Education and Research; Institutional Ethics Committee of BLDE (Deemed to be University) Shri B M Medical College. Institutional Ethics Committee, Karnataka Institute of Medical Sciences (KIMS); Institutional Ethical Committee, the Karnataka Cancer Therapy and Research Institute. The trial was approved by the Health Ministry's Screening Committee with the Indian Council of Medical Research (ICMR) acting as its Secretariat.

CLINICAL TRIAL REGISTRATION

India CTRI/2019/01/017289. ClinicalTrials.Gov number NCT04154644.

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APPENDIX 1

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